REMARKS

This Amendment is in reply to the Office Action mailed September 7, 2005. Applicants have reviewed the Office Action and have the following comments.

Applicants thank the Examiner for his withdrawal of the finality of the previous Office Action and of all rejections made in such Office Action.

Claim 16 has been amended to replace the term "neuroprotectant" with "brimonidine". This amendment is supported by the specification at, e.g., original claim 37.

Rejection Pursuant to 35 U.S.C. §112(1)

The Office Action of January 19, 2006 has rejected claim 16, 18-22 and 30 as being indefinite for lack of antecedent basis for the term "said neuroprotectant" in claim 16, the sole independent claim. The Examiner is correct in this allegation, and Applicants regret any inconvenience this lack may have caused.

Claim 16 has been now been amended to delete the term "neuroprotectant" and instead make reference to brimonidine, for which reference there is antecedent basis in claim 16. For this reason, the rejection is now moot.

Rejection Pursuant to 35 U.S.C. §103(a)

The January 19th Office Action has rejected claims 16, 18-22 and 30 as being allegedly obvious over U.S. Patent Application 2002/0040015, to Miller et al., in view first of Granville, (U.S.

Patent No. 6,180,402), and further in view of Wheeler et al., EUR. J. OPHTHAL. 9:S17-S21 (1999). Applicants respectfully traverse this rejection for the following reasons.

To establish a *prima facie* case of obviousness, an Office Action must first provide evidence of some suggestion or motivation to modify the references or to combine the reference teachings. Second, the Office Action must show that the person of skill in the art would have had a reasonable expectation of success if the suggestion were followed. Lastly, the prior art reference(s) must teach or suggest all the claim limitations. See e.g., Manual of Patent Examining Procedure (MPEP) § 2143.

Hindsight reconstruction of a claimed invention to find obviousness is always improper. Obviousness must be shown by the suggestions and teachings of the prior art, rather than simply their disembodied content.

Finally, in a proper obviousness analysis, the invention must be considered as a whole. "[T]hat all elements of an invention may have been old (the normal situation), or some old and some new, or all new, is however, simply irrelevant. Virtually all inventions are combinations and virtually all are combinations of old elements. A court must consider what the prior art as a whole would have suggested to one skilled in the art." *Environmental Designs, Ltd. v. Union Oil Co.*, 218 USPQ 865 (Fed. Cir. 1983)(emphasis added).

The January 19, 2005 Office Action again applies Miller et al., U.S. Patent Publication 2002/0040015 against the presently pending claims. Applicants gratefully acknowledge the Examiner's agreement that the priority date for the anti-apoptotic agents of Miller is not the February 10th, 2000 filing date of the provisional patent application, but rather the February 9, 2001 filing date of the non-provisional patent application.

However, with respect, the Applicants submit that under the present facts the use of the Miller et al., U.S. Patent Publication 2002/0040015 is improper. When, as here, there exists a provisional patent application filed before the date of constructive reduction to practice of the present invention (Serial No. 60/181,641, of record in the prosecution of this application), and when such provisional application defines exactly the disclosure (to be considered as a whole) that may be considered in an obviousness analysis, it is improper to use the later filed application subsequently published as U.S. Patent Publication 2002/0040015 as the basis for a rejection.

This is a critical point. The January 19, 2006 Office Action states "with respect to using an anti-angiogenic factor, Miller has an effective filing date of 2/10/2000", and for the sake of argument, Applicants do not presently dispute this. However, despite the fact that the Applicants and Examiner agree that the effective filing date for the anti-apoptotic agents of Miller is February 9, 2001, the February 10, 2000 provisional application is not silent on the use of apoptosis modulating agents.

The Miller provisional application does contain disclosure concerning apoptosis, and such disclosure must be considered as part of the teaching of the Miller reference, and thus part of the state of the art at the filing date of the present application. To the extent that the later filed non-provisional application presently cited does not contain this disclosure, the January 19, 2006 Office Action fails to consider the teachings of the 2/10/2000 provisional application as a whole.

And what is the nature of the teachings of the Miller provisional application regarding apoptosis? On page 4 of the Miller provisional 60/181,641 the application states:

> In another aspect, the invention provides a method of treating unwanted choroidal neovasculature. The method comprises the steps of: (a) administering to a primate in need of such treatment, an apoptosis-inducing factor in an amount sufficient to permit an effective amount to localize in the choroidal neovasculature; administering to the primate an amount of a photosensitizer sufficient to permit an effective amount of [sic] localize in the choroidal neovasculature; and (c) irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature. Cytotoxicity of the PDT can be enhanced relative to a similar treatment lacking the apoptosis-inducing factor, thereby enhancing occlusion of the choroidal vasculature.

(emphasis added).

Further explanation for the rationale of using pro-apoptotic agents in PDT is provided e.g., on page 11 of the Miller provisional application:

> Different apoptotic pathways appear to be triggered by PDT in BRCE [bovine retinal capillary epithelium] and RPE [retinal pigmented epithelium]. It is contemplated that by specifically priming the apoptotic machinery of neovascular endothelial cells prior to PDT it may be possible to increase their sensitivity to PTD. This approach could reduce the light dose (fluence) required to achieve CNV [choroidal neovasculature] closure and thereby decrease the effect on surrounding cells such as RPE."

(emphasis added).

Thus, whatever its teachings concerning PDT and angiogenesis, the Miller provisional application actually teaches away from using an anti-apoptotic agent in conjunction with PDT, and certainly provides no motivation for one of skill in the art to make the present invention comprising these use of PDT in conjunction with a neuroprotectant (brimonidine).

The January 19, 2005 Office Action also cites Granville et al., U.S. Patent 6,189,402 (filed Nov. 20, 1996) as teaching that it is beneficial to include an anti-apoptotic molecule in PDT treatments.

Specifically, Granville discloses the use of serine and cysteine protease inhibitors in conjunction with PDT to prevent cleavage of the inactive zymogen of the enzyme CPP32 to the activated CPP32 protease, thus inhibiting the induction cascade resulting in apoptosis.

However, Granville also makes clear that "the inhibition of apoptosis is also target cell dependent." Granville at column 3, line 4. Indeed, Granville discloses that certain agents that are "powerful inducers" of apoptosis in one cell type "have also been classified as apoptosis inhibitors" in many other cells. *Id.* at lines 5-7.

In light of this ambiguity, Granville et al. illustrate their invention using the HL-60 promyelocytic leukemia cell line (see Granville, Examples 1 and 2), and refer to another test of apoptosis using the megakaryoblastic cell line CMK. Granville, column 8, line 21. Thus, both such cell lines are of blood cell lineage. Granville does not disclose or suggest the use of neuroprotectants (agents that selectively protect neural cells from injury, including apoptosis) such as brimonidine, nor is it clear whether the anti-apoptotic agents disclosed by Granville would stimulate or inhibit apoptosis in neural cells. Indeed, given the target cell dependency acknowledged and discussed by Granville (and referenced above), one of ordinary skill in the art is left with the impression that the blood cell types are the ones that are important to target for inhibition of CPP32 protease activity.

The combination of Granville (which was filed in 1996) and the Miller provisional (filed in 2000), therefore reflect opposition teachings. As research usually follows a temporal progression, the implication is that the disclosure of Granville may reflect an early and untested rationale, and that the

disclosure of Miller et al. four years later probably represents a more current understanding of the state of the art at the time of filing the present application. Given that these references are in conflict as to the best way to preserve visual acuity using PDT, there can be no consensus inferred from the combination of these references; they reflect confusion in the state of the art at the date of filing the present application, or indeed, may reflect that those of skill in the art now though stimulating apoptosis during and after PDT was preferable to inhibiting it.

It is this confused state of the art that Wheeler must be considered. The January 19, 2006 Office Action cites Wheeler as teaching that brimonidine is an anti-apoptotic neuroprotective alpha 2 agonist compound. Therefore, the Office Action concludes, it would have been *prima facie* obvious to one of skill in the art to perform the method of Granville and substitute brimonidine as the neuroprotective agent.

The presently pending claims are drawn to methods of protecting ocular neurons from damage during PDT treatment comprising the administration of a neuroprotectant amount of the alpha 2 agonist brimonidine. Neuroprotection is not mentioned or suggested in either the Miller provisional application or in Granville. What the Miller provisional and Granville do make clear is that there were myriad ideas about how to improve the efficacy of PDT before the filing date of the present application, and that these ideas ranged from the induction of apoptosis to the inhibition of apoptosis.

The relevance of Wheeler et al., EUR. J. OPHTHAL. 9:S17-S21 (1999) in the context of the presently claimed invention must be determined in such an environment, keeping in mind that when performing an obviousness analysis, the claimed invention must be considered as a whole, the references must be considered as a

whole and must suggest the desirability of making the combination, the references must be viewed without the benefit of hindsight, and the person of skill in the art must have a reasonable expectation of success. M.P.E.P. 2141(II).

Without knowing what is taught by the present specification or what has been discovered in the past six years of research in this art, it is clear that the person of ordinary skill in the art could not have had a reasonable expectation of success in the use of brimonidine, a member of a class of compounds (alpha 2 agonists; neuroprotectants) not even mentioned by either of the other cited references. Nor does Wheeler discuss the desirability of using brimonidine or other neuroprotectants in PDT.

The Office Action states that brimonidine is an art-recognized equivalent of the anti-apoptotic agents of Granville. See Office Action page 5. However, M.P.E.P. 2144.06 states "in order to rely on equivalence as a rationale supporting an obviousness rejection the equivalency must be recognized in the prior art and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents." Indeed, Granville is drawn to the use of protease inhibitors which block cell death signals, while brimonidine appears to act by enhancing neuron-specific intrinsic signaling pathways that are selectively mediated by the alpha 2 adrenergic receptor. See Wheeler, Introduction. It is neither legally or scientifically obvious that this effect (employing the biochemistry of the target cells themselves to survive apoptotic signaling) would function in PDT, being a wholly different means of inhibiting apoptosis than described in Granville.

Thus, at the very most (and despite the lack of any suggesting in Miller or Granville) a person of skill in the art might be curious as to whether brimonidine would be useful in PDT

therapy. However, such a person could have had no reasonable expectation of success in satisfying this curiosity. A mere possibility that experimentation might yield interesting results does not satisfy the inquiry 35 USC §103(a), which requires much more to establish a *prima facie* case of obviousness.

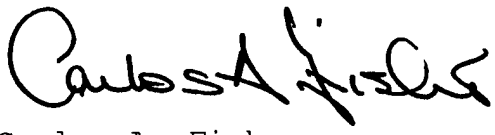
For these reason the Applicants respectfully request reconsideration and withdrawal of the present rejections.

CONCLUSION

For the reasons given above, the claims are now thought to be in condition for allowance, and a Notice to that effect is earnestly sought.

No fee is thought due in connection with this communication. However, if Applicants are in error with regard to this point, please use Deposit Account 01-0885 for the payment of any such fee now due, or to credit any overpayment.

Respectfully submitted,



Carlos A. Fisher
Registration No. 36,510